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Review Article

Developmental Dynamics of the Cardiovascular System: A Cellular Perspective

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ABSTRACT

The development of the cardiovascular system exemplifies the complexity of embryonic morphogenesis, showcasing a finely tuned sequence of cellular and molecular events. As the first functional organ system in the embryo, the heart plays a pivotal role, serving as a model to explore cellular origins, lineage diversification, and the signaling pathways essential for cardiac maturation. This study provides an in-depth examination of the major cellular contributors, including cardiac progenitor cells, neural crest outflow tract cells, endothelial cells, smooth muscle cells, and cardiac fibroblasts, all of which are critical for the proper formation and function of the cardiovascular system. We highlight the integration of cell-specific signals and gene regulatory networks that drive key developmental processes, from cardiac morphogenesis to the establishment of vascular connections. This review underscores the physiological significance of cellular interactions in heart development and offers insights that may inform therapeutic strategies for cardiovascular anomalies.

1. EARLY EMBRYONIC ORIGIN OF CARDIOVASCULAR SYSTEM

From the earliest stages of life, the circulation of body fluids is essential. It is necessary to deliver oxygen and nutrients to the body surface, internal cells, and tissues, particularly the contractile tissues of the body (Edgar *et al.*, 2013). The ability of an animal to perform different functions depends upon the efficiency of its circulation system. Active animals generally possess more efficient circulatory systems than less active organisms. In vertebrates, circulation depends upon a system, the cardiovascular system. This system starts functioning during embryonic development, and the heart is the first functional organ. In humans, cardiovascular system is composed of compartmental heart, blood, blood vessels and lymphatic system (Clark, 2015). The heart itself is an organ, under the influence of different mechanisms like nervous, mechanical and chemical. According to the great philosopher, Aristotle "Heart is the center of man". Moreover, Father of physiology, Galen said "Heart sets the blood in motion" (Opie, 2004). In 1628, William Harvey, gave the basic concept of blood circulation due to pumping of heart (Harvey, 1889; Androutsos *et al.*, 2012).

In the morphogenesis of heart, the first step is specification of cardiac cell fate. Second step is the looping of the heart tube. Heart looping leads to segmentation and growth of the heart chambers. Proper function and division of the heart chambers affirm by the formation of cardiac valve. The last step of heart morphogenesis is connection of the vascular system with the heart (Table 1, Figure 1).

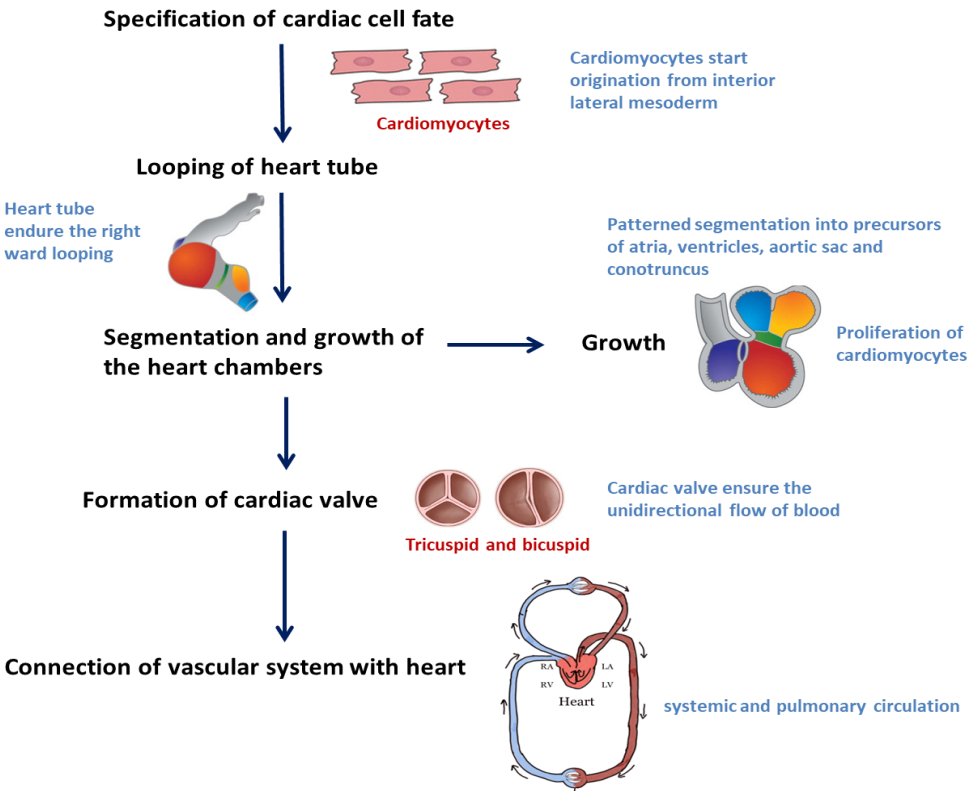


Figure 1. Cardiac morphogenesis - precisely orchestrated series of steps

Table 1. Stages of cardiac morphogenesis and associated genes

Stages of cardiac morphogenesis	**Genes**	**References**
Specification of cardiac cell fate	*MLC2v, SERCA2a, b-MHC, Nkx2-5, Bmp2, Smad1*	(Christoffels *et al.*, 2000) (Prall *et al.*, 2007)
Looping of heart tube	*MesP1, GATA4*	(Saga *et al.*, 1999), (Kuo *et al.*, 1997; Molkentin *et al.*, 1997),
Segmentation and growth of the heart chambers	*ANF, Chisel, Connexin 43, Irx5, b-MHC, Hand1, Tbx5*	(Christoffels *et al.*, 2000)
Formation of cardiac valve	Sox9, NF-ATc	(Akiyama *et al.*, 2004), (Ranger *et al.*, 1998)
Connection of vascular system with heart	*ET-1, dHAND, neuropilin-1, Mfh1, RAR/RXR, bHLH, gridlock, TFAP2B*	(Srivastava and Olson, 2000)

2. CARDIOGENIC LAYERS DEVELOPMENT

Early embryonic tissues consist of four types, the zygote, inner cell mass, epiblast, and primitive streak. Another type of tissue is extraembryonic tissue that included trophoblast, hypoblast and extraembryonic mesoderm. Gastrulation derivatives included ectoderm, mesoderm, endoderm, neural crest, paraxial mesoderm, intermediate mesoderm: and lateral mesoderm. On the 12th day of fertilization, the embryo gets implanted in the uterus, primitive streak formed and the process to form germ layers, initiated. For heart morphogenesis, two layers actively participate, ectoderm and mesoderm. After leaving the primitive streak, mesodermal cells gradually form paraxial and lateral mesoderm. During 17th to 18th week, lateral mesoderm split into two layers, somatopleuric mesoderm and splanchnopleuric mesoderm (Iaizzo, 2009). In the primary heart field, splanchnopleuric mesoderm contains endocardial and myocardial cardiogenic precursors (O'sullivan *et al.*, 2010). Adjacent to the neural tube and notochord lies the paraxial mesoderm. In addition to contributing to the development of the head, skull, and muscles, it also plays a role in heart development (Tam and Trainor, 1994; Parker *et al.*, 2003). Neural crest generates a broader array of cells and tissue during development. Neural crest cells are sometimes referred to as a 'fourth germ layer' due to their broad differentiation potential. Marianne Bronner-Fraser explored collection of 83 genes expressed as a consequence of neural crest induction (Gammill and Bronner-Fraser, 2002). The cardiac neural crest, derived from the neural crest, plays a crucial role in the formation of the heart's smooth muscle, the outflow tract, the septum, and the walls of the aorta and aortic arch–derived arteries (Stoller and Epstein, 2005).

3. CARDIAC PROGENITOR POPULATIONS

Cardiac progenitor cells originate from the mesoderm and subsequently differentiate into the myocardium and endocardium (Le and Chong, 2016). They are also known as the cardiogenic mesoderm progenitors and pre cardiac cells. Genes involved in this process are *MESP1, NKX2-5* and *SMARCD3*(Devine *et al.*, 2014; Den Hartogh *et al.*, 2016). Fibroblast growth factor 8 (FGF8) and bone morphogenetic proteins (BMPs) are key signaling molecules that play a significant role in the differentiation of cardiac progenitor cells (Brand, 2003; Xin *et al.*, 2013). From these progenitor cells, pre-endocardial cells arise, which subsequently develop into the endocardium of the heart. Endocardial cells are therefore descendants of pre-endocardial cells (Kirby, 2007). Another type of cells involved in the cardiogenic mesoderm are *pre-myocardial Cells.* These cells are also known as pre-cardiomyocytes. Bone morpho-genic protein (BMPs), Dickkopf related protein 1 (Dkk1) and Fibroblast growth factor (FGF) are the signals which are important for the differentiation of Pre-myocardial Cells (Fakhry *et al.*, 2005; Kruithof *et al.*, 2006). Genes associated with Dickkopf related protein are the family of 4 genes *Dkk-1* to *Dkk-4*(Niehrs, 2006). Pro-epicardial progenitor cells arise from the lateral mesoderm and develop into the pro-epicardium. These adherent cells initially migrate to the surface of the heart to form the epicardial layer. Subsequently, they migrate into the heart, where they give rise to precursor cells that contribute to the formation of the coronary vessels. (Brade *et al.*, 2013). Ets1 (Ets-1) induced signals are required for the differentiation of pro-epicardial progenitor cells (Hashiya *et al.*, 2004). At the prenatal stage, a double walled sac enclosing the heart and root of all vessels is formed known as pericardium. The pericardium consists of two layers: an inner visceral layer and an outer

parietal layer, with pericardial fluid in the intervening space. Epicardial cells are involved in the formation of the pericardium (Rodriguez and Tan, 2017). Lars Bochmann reported a number of epicardial signature genes including *UPK3B,GPM6A, DMKN, KRT8, C3, C3 and TBX18 (Bochmann et al., 2010).*

The outflow tract epicardium of the heart is formed by elongated outflow epicardial progenitor cells. These progenitor cells originate from the splanchnopleuric mesoderm. The cardiac outflow tract cushions are formed by neural crest–derived outflow tract cells (Engleka *et al.*, 2012). Origin of these cells is neural crest. WNT signaling is required for cell proliferation, whereas semaphorin (SEMA3C) signaling is required for cell migration (Scholl and Kirby, 2009). *Cardiomyocytes* are also involved in the formation of the outflow tract and originate from the secondary heart field cells. For the proliferation of Cardiomyocytes, Tbx1 Induced signals are required. For the differentiation, BMPs, Isl1 Induced and Wnt11 signals are required (Buckingham *et al.*, 2005; Dyer and Kirby, 2009). *Inflow progenitors* are very important cells as they are the ancestor of several heart cells including cardiomyocytes of left, right atrium as well as of left ventricle. Sinoatrial Node Cells of Sinoatrial Node and Atrioventricular node cells are derived from inflow progenitors. Retinoic acid is an important signaling molecule that regulates the differentiation of these inflow progenitors (Ryckebusch *et al.*, 2008). Three CYP26 genes, *Cyp26a1, Cyp26b1*, and *Cyp26c1*, have been identified as regulators of RA homeostasis (Nakajima, 2019). Endocardial tube cells form the inner lining of the heart and are continuous with the blood vessels. These cells play an important role in the development of endocardium.

1.1 Myocardium Development

The myocardium is separated from the endocardium by an acellular, gelatinous matrix known as cardiac jelly. The development of the myocardium requires the coordinated activity of various genes including *MYLK3, GPR37L1, GPR35, MMP23*, and *NBC1(Min et al., 2010)* as well as multiple cell types such as cardiomyocyte progenitor cells, cardiomyocytes, cardiac fibroblasts, and mature cardiac fibroblasts. Cardiomyocyte Progenitor Cells are also known as *cardioblasts*. These are the ancestors of myocardium Cardiomyocytes and cardiac crescent cells (Wu *et al.*, 2008). Several signals are required for the differentiation of these cells, including BBMPs, Dkk1, FGF8, Nodal, Wnt11, SHH and FGF. On the other hand, Notch1 and WNTs are the inhibitors of differentiation (Shi *et al.*, 2000; Abu-Issa and Kirby, 2007). *Cardiomyocytes of the myocardium* give rise to various cell populations, including those contributing to the right ventricle, Atrioventricular septum, atrial septum, outflow tract, left and right atria, heart tube, ventricular septum, vascular smooth muscle cells, and the aortic arch arteries. For the Proliferation of myocardium cardiomyocytes various signals required including BMP10, FGF9, FGFs, Foxc1 (Mf1), Foxc2 Induced, RA, SHH, Tbx1 Induced and WNTs. While for the differentiation, *FGF8, Foxh1 Induced, Gata4, Isl1, Tbx20 Induced, Gata4, Nkx2-5, Srf, Tbx5 Induced and Tbx20 Induced* genetic signals are required. Additionally, Isl1 induced signals are required for migration of cells (Martin-Puig *et al.*, 2008). *Cardiac fibroblasts* are essential for maintaining the myocardium. They are derived from epicardial progenitor cells and play a significant role in the myocardial walls by providing structural support as a scaffold. These cells are also known as *interstitial fibroblasts*. PDFG receptors are present on cardiac fibroblasts for the action of *PDGFRA* (CD140a) Induced signals (Smith *et al.*, 2011). Another important cell type that plays a crucial role in myocardial development is the *mature cardiac fibroblast*, which is derived from cardiac fibroblasts. These cells, along with

cardiomyocytes, are distributed throughout the heart and together account for up to two-thirds of the cell population in the adult heart (Ieda *et al.*, 2009).

1.2 Endocardium Development

The innermost layer of the tissue that mostly covers the chambers of the heart is *endocardium***.** It is the endothelial lining of the heart. Varieties of cells constitute endocardium, and their heterogeneity makes endocardium capable of forming a diversified inner part of the heart (Delaughter *et al.*, 2011). In the formation of cardiac valves and septa of the heart, endocardium plays a critical role. After passing various steps of differentiation *endocardial cells* form, from cardiac progenitor cells with the genetic actions of NFATc1. GATA4, GATA5 and Nkx2-5 (Harris and Black, 2010). Myocardial growth is regulated by proteins secreted by endocardial cells. Angiopoietin signaling is involved in the differentiation of endocardial cells. These cells are precursors of endocardial tube cells and cushion mesenchymal cells (Harris and Black, 2010). Cushion mesenchymal cells arise through the proliferation of endothelial cells, and their cytoplasm resembles that of endothelial cells. These cushions are the precursors of heart valves, initially swelling but later develop into thin leaflets and prevent regurgitation of blood in the heart. Cushion mesenchymal cells are the ancestor of endocardial cushion cells and outflow tract cushion. Last but not least, cells that participate in the development of endocardium are *endocardial tube cells.* These are the ancestors of the endocardial tube cell of outflow tract and Atrioventricular Canal (Person *et al.*, 2005).

1.3 Epicardium Development

Epicardial progenitor cells play a crucial role in the formation of the heart's epicardium. They give rise to three cell types involved in epicardial development: mesenchymal cells, sub-epicardial cells, and angioblasts. A previous study reported expressions of *Wt1, Tbx18, Gata5, Tcf21, Scx*, and *Sema3d* in the epicardium (Quijada *et al.*, 2020) . Epicardial progenitor cells are polygonal in shape, and these cells need Platelet derived growth factors (PDGFs) and vascular endothelial growth factors (VEGFs) for their differentiation. PDGFRβ signaling has a role in instructing epicardial cells for the migration into myocardium (Mellgren *et al.*, 2008). A space known as the sub-epicardial space forms between the epicardium and the myocardium. This sub-epicardial space specifically is populated by the *sub-epicardial cells* and *mesenchymal cells*. Extracellular matrix is densely populated by sub-epicardial cells, whereas mesenchymal cells are particularly abundant at atrioventricular junction. Mesenchymal cells require several signals for their differentiation including PDGFs, VEGFs, FGFs and TGFβ1. Moreover, mesenchymal cells are the ancestor of Angioblasts, Cardiac Fibroblasts and Vascular Smooth Muscle Cells. *Angioblasts* developed from the mesenchymal Cells give rise to another type of cells known as capillary endothelial cells (Smith *et al.*, 2011).

4. CARDIAC VALVES

The atrioventricular valves are formed by the proliferation of *cushion mesenchymal cells* and close the atrioventricular septum and lead to the valve leaflets formation. As the valve primordium matures, proliferation of cushion mesenchymal cells decreases. At the end of this process, the Atrioventricular valves develop into the bicuspid and tricuspid valves. The bicuspid valve forms between the left atrium and ventricle, while the tricuspid valve is located between the right atrium and ventricle. Fully formed valves can be observed by approximately day 63 of embryonic development. *Atrioventricular valve cells* are involved in valve formation, and they are developed from the cardiomyocytes of

atrioventricular septum. Bone morphogenetic protein (BMP) inhibition is part of valve formation and requires inhibitory Smad6 (De Vinuesa *et al.*, 2016). Other valves in the cardiovascular system are semilunar valves and are half-moon shaped. Semilunar valves are the leaflets of connective tissue and endocardium. These are situated in two places, first between the left ventricle and aorta and secondly between right ventricle and pulmonary artery. These valves prevent the backflow of blood from the arteries into the ventricles. Semilunar valves differ from atrioventricular valves, as they do not have chordae tendineae (Goodwin and Biechler, 2019). *Semilunar valve cells* originate from the cushion cells and form the semilunar valves. Bone morphogenetic protein (BMP) including BMP2, BMP4 and BMP6 secreted by these cells (Goodwin and Biechler, 2019). According to the previously published data BMP controls the expression of 203 genes (105 up-regulated and 98 down-regulated) (Peng *et al.*, 2003).

A clear division of the heart into four chambers is made possible by the *atrioventricular canal*. It develops through the formation of a constriction between the atrium and ventricle. The canal also marks the future sites where the Atrioventricular valves will form. *Atrioventricular canal* and *endocardial tube cells* play significant roles in the formation of canal systems. Atrioventricular canal cells are descendants of heart tube cells. Proximally to the Atrioventricular valves and ventricles, Atrioventricular canal cells form the smooth walled rim (Vrljicak *et al.*, 2012). During the development of embryo, the atrioventricular (AV) canal divides into left and right canals. Right AV broadens to the right side, allowing blood passing to the presumptive right atrium and right ventricle. Left AV broadens toward the right side of the heart allowing blood passing in the left side of heart (Calabrò and Limongelli, 2006).

5. CARDIAC CONDUCTION

Slow conducting system of the heart has two types of nodes, Sinoatrial Node and Atrioventricular node. The first node in the cardiovascular system is the sinoatrial (SA) node, also known as the pacemaker of the heart. It is located at the junction of the right atrium and the superior vena cava. It regulates and coordinates heart contractions by generating electrical impulses. The generated impulses cause the contraction of atria. *Sinoatrial node cells* are distinct from other cells as they have elongated nuclei and are rich in glycogen. These are comparatively smaller than other working atrial myocytes. Shox2 induced signals inhibit the Nkx2-5 activity and promote the differentiation of Sinoatrial node cells (Mommersteeg *et al.*, 2007). The *atrioventricular node* is located at the junction between the atria and ventricles, at the base of the atrial septum. It plays a crucial role in transmitting electrical impulses from the atria to the ventricles. It is also known as the slow conducting AV node as it receives the initial pulse from the sinoatrial node and regulates it by slowing down the impulses then passes to the ventricle myocardium. *Atrioventricular node cells* (secondary pacemaker center) involve the formation of AV nodes. These cells develop from the Atrioventricular canal cells (Van Weerd and Christoffels, 2016). *Ventricular conductive cells* and *His bundle cells* form the fast-conducting system of heart. Ventricular Conductive Cells are the ancestor of three types of cells Bundle Branch Cells, His Bundle Cells and Purkinje Fiber Cells. Purkinje fibers form a network that receives conduction signals from the atrioventricular node (Poelmann, 2024). By stimulating ventricle myocardium, it can also activate right and left ventricles. *Purkinje fiber cells* facilitate the rapid impulse conduction due to their two key features, having gap junctions and wide diameters (Coromilas *et al.*, 2019).

6. AORTA

During early embryonic development, paired dorsal aortae are present bilaterally. Through remodeling, these paired vessels fuse to form a single dorsal aorta, which is later divided into thoracic and abdominal segments. *Arterial endothelial cells* and *vascular smooth muscle cells* are required for the formation of dorsal aorta. The wall of dorsal aorta is lined by the vascular smooth muscle cells which are derived from different somite compartments. These cells first migrate towards the ventrolateral wall and later circle the aorta (Esner *et al.*, 2006; Sawada *et al.*, 2018). Arterial endothelial cell originating from angioblasts also contribute to the lining of aorta (Atkins *et al.*, 2011). At the arterial pole of the heart, an aortic sac is situated and acts as a collecting point for all blood vessels passing from this point (Subramanyan *et al.*, 2023). In the fully developed heart, the arterial pole is located at the base of the pulmonary trunk and the aorta. The formation of the definitive *arterial pole* requires contributions from both myocardial and smooth muscle cells. *Neural crest outflow tract cells, cardiomyocytes and endocardial tube cells* participated in the formation of arterial pole. Another pole of heart is venous pole (Abie *et al.*, 2024). This pole arises from myocardial cells and situates at pulmonary vein and early superior vena cava. Expression of several genes contribute to the development of this part of the cardiac system (Sahai-Hernandez *et al.*, 2023).

7. CARDIAC CHAMBERS

The heart is a hollow, four-chambered organ composed of thick-walled ventricles and thin-walled atria. The ventricles are primarily responsible for pumping blood, while the atria serve as receiving chambers for blood returning to the heart from the body (Lewis, 2019). Oxygenated blood from the pulmonary vein comes to the Left atrium and then goes to the left ventricle. Deoxygenated blood from two vena cavas comes to the right atrium and goes to the right ventricles (Venkatram, 2024). Atrium of the heart is populated by two types of cells, *cardiomyocytes* and *mature cardiomyocytes*. Cardiomyocytes of the atrium develop from the inflow progenitors and then finally form mature cardiomyocytes. *Gata4, Nkx2-5, Srf, Tbx5* Induced signals are required for the differentiation of atrium's cardiomyocytes. Right ventricle is also known as the pulmonary ventricle because it pumps deoxygenated blood to the lungs while the left ventricle receives oxygenated blood and pumps it to the aorta (Demyanets, 2024). In the ventricle of heart other than *cardiomyocytes* and *mature cardiomyocytes, ventricular conductive cells* are also present (Kirby, 2007).

By means of aorticopulmonary septum, arterial blood flow is divided into systemic and pulmonary blood streams. *Aorticopulmonary septum cells*, derived from the cardiac neural crest cells, are involved in the formation of septum (Meilhac and Buckingham, 2018). Atrioventricular canal is divided by the atrioventricular septum. After condensation and fusion, the atrioventricular endocardial cushions undergo condensation, fusion, and remodeling, to form the valve leaflets and supporting structures. Atrioventricular valve leaflets have distinct layers called *atrialis*. Cardiomyocytes of Atrioventricular septum required *Nkx2-5 and Tbx2* Induced signals (Driscoll, 2016). During the 7th week of human development, the atrial septum is formed. There are two types of atrial septa: the primary atrial septum and the secondary atrial septum. The first one originated from the myocardium and elongated to the Atrioventricular cushions and divided into two atrial chambers. Secondary septum forms to the right side of the primary atrial septum and populated by the atrial cardiomyocytes (Anderson *et al.*, 2002). The interventricular septum is a thick wall that divides the ventricle into left and right

chambers and contains *ventricular septum cells*. These cells also develop from the cardiomyocytes of the myocardium (Kuusela, 2018).

8. CONCLUSION

The cardiovascular system exemplifies the complexity and precision of human embryonic development. Understanding the origins and differentiation of key cardiac cell types, together with the signaling pathways that regulate these processes, provides essential insights into both normal and abnormal heart development. This knowledge has important clinical implications, particularly for improving the diagnosis and treatment of congenital heart defects and other cardiovascular disorders.

Furthermore, a deeper understanding of cardiac cell lineage and developmental signaling pathways is increasingly shaping the field of regenerative medicine, including efforts to engineer cardiac tissue and develop cell-based therapies for heart repair. Continued research in this area also offers promising directions for future studies, such as refining stem cell–based approaches, enhancing in vitro heart models, and improving strategies for myocardial regeneration. Ultimately, these advances have the potential to significantly improve cardiovascular health outcomes.

Declarations

Conflict of interest
There is no conflict of interests.

Author Contributions
SS: Formal analysis, Writing – original draft. **S:** Conceptualization, Writing – review & editing.

Ethics Approval
No ethical approval was required for this study as it did not involve human or animal subjects.

Generative AI Disclosure
The authors declare that generative artificial intelligence tools were used solely to assist with language editing, including correcting grammatical errors and improving sentence clarity. No AI tools were used to generate scientific content.

Availability of data and material
Not Applicable

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